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Review

γδ T cell responses: How many ligands will it take till we know?

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ABSTRACT

γδ T cells constitute a sizeable and non-redundant fraction of the total T cell pool in all jawed vertebrates, but in contrast to conventional αβ T cells they are not restricted by classical MHC molecules. Progress in our understanding of the role of γδ T cells in the immune system has been hampered, and is being hampered, by the considerable lack of knowledge regarding the antigens γδ T cells respond to. The past few years have seen a wealth of data regarding the TCR repertoires of distinct γδ T cell populations and a growing list of confirmed and proposed molecules that are recognised by γδ T cells in different species. Yet, the physiological contexts underlying the often restricted TCR usage and the chemical diversity of γδ T cell ligands remain largely unclear, and only few structural studies have confirmed direct ligand recognition by the TCR. We here review the latest progress in the identification and validation of putative γδ T cell ligands and discuss the implications of such findings for γδ T cell responses in health and disease.

Contents

Abbreviations: APC, antigen presenting cell; BTN3, butyrophilin 3 (CD277); Btnl/BTNL, butyrophilin-like; CDR, complementarity determining region; CMV, cytomegalovirus; DC, dendritic cell; DETC, dendritic epidermal T cell; EPCR, endothelial protein C receptor; HMB-PP, (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; IPP, isopentenyl pyrophosphate; MHC, major histocompatibility complex; MICA, MHC complex class I chain-related protein A; MR1, MHC related protein 1; TCR, T cell receptor.

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1. Introduction: how does it feel, like a complete unknown?

The past three decades have witnessed remarkable progress in our understanding of antigen presentation and the molecular and cellular mechanisms underlying antigen-specific αβ T cell responses, as summarised in this special issue of *Seminars in Cell and Developmental Biology*. The outstanding importance of antigen presentation for biomedical science as a whole of some of the major contributions in the field is best illustrated by the awarding of the Nobel Prizes in Physiology or Medicine for the discovery of the major histocompatibility complex (MHC) in 1980, the principles of overcoming organ transplant rejection in 1990, the definition of MHC restricted immune responses in 1996, and the discovery of dendritic cells (DCs) and their role in adaptive immunity in 2011. Such knowledge is now successfully exploited in the clinic for antigen-specific vaccination against infectious diseases and cancer, and for the induction of immune tolerance in autoimmune disorders.

Set apart from MHC restricted αβ T cells, γδ T cells constitute a sizeable and non-redundant fraction of the total T cell pool in all jawed vertebrates. Although typically portrayed as a minor lymphocyte subset in humans and rodents, γδ T cells may actually exceed >50% of all T cells and thus constitute the dominant T cell population in certain tissues and species, for instance in ruminants and chicken (especially in early life), in the mouse epidermis, and in human blood during microbial infection [1–3]. Moreover, γδ T cells have been implicated in a wide range of immunological scenarios in the healthy organism and in disease [4–6]. However, progress in our understanding of the role of γδ T cells in the immune system has been hampered, and is being hampered, by the considerable lack of knowledge regarding the structures γδ T cells respond to, despite extensive efforts by numerous laboratories since the discovery of γδ T cells in the mid-1980s [7]. In stark contrast to the well-defined presentation of peptide antigens to $CD4^+$ and $CD8^+$ αβ T cells via MHC class II and class I molecules, respectively, and the elucidation of additional pathways leading to the presentation of lipids and metabolites via CD1 family members and the MHC-related protein MR1 [8], there is no consensus as to the class of 'antigens' γδ T cells recognise, and how such antigens are presented. In fact, there is only little evidence that antigens are indeed 'presented' to γδ T cells in the classical sense.

2. The role of the γδ TCR: blowin' in the wind

2.1. Ligand recognition during thymic selection

As in αβ T cells, a diverse TCR repertoire can be generated in γδ T cells by variable (V) gene combinations and formation of V(D)J junctions [6]. γδ T cells are conspicuously different at the TCR level from conventional αβ T cells in that they display characteristic TCR biases with regard to V usage and/or complementarity determining region 3 (CDR3) sequences, depending on the anatomical location and physiological context. Of note, there are no obvious homologies between human and mouse V gene sequences, thus making it difficult to compare mouse and human γδ T cells based on their TCR usage [11,12]. In mice, distinct waves of γδ T cell subsets expressing characteristic Vγ and Vδ combinations populate different organs during embryonic development and display distinct effector functions [4–6]. These early γδ T cells in fact express invariant γδ TCRs, whereas later on in development the TCRs possess polyclonal CDR3 sequences but typically still show biased V chain usages [14].

Representing the prime example of such an invariant TCR, the first γδ T cells to emerge in the murine foetal thymus express a fixed TCR composed of invariant Vγ5Jγ1Cγ1 and invariant Vδ1Dδ2Jδ2 chains (Vγ5/Vδ1 in short; nomenclature according to Heilig and Tonegawa [13]) and migrate to the skin epidermis where they become dendritic epidermal T cells (DETCs) [14]. The next such population arising in the thymus actually carries the same canonical Vδ1Dδ2Jδ2 chain yet combined with an invariant Vγ6Jγ1Cγ1 chain (Vγ6/Vδ1 T cells), and seeds the skin dermis and other tissues [14]. Thus, separate γδ T cell subsets may occupy different sites even within the same organ.

The biases in TCR usage depending on anatomical locations and functions strongly indicate a direct involvement of the TCR, and consequently of tissue-restricted self or non-self ligands, in shaping different γδ T cell compartments and in local immune surveillance and/or pathogen sensing. However, it has been suggested that γδ T cells may also exert major functions in an innate-like, TCR independent manner [15,16]. Such findings seemingly question the physiological relevance of the γδ TCR and the corresponding γδ T cell ligands in certain contexts although it may be technically challenging to exclude simultaneous TCR triggering depending on the experimental conditions [17]. There is also apparently conflicting evidence for the precise role of the γδ TCR in thymic development, especially with regard to the requirement of a possible ligand-dependent positive selection and developmental programming of γδ T cells [18]. Clearly, the role of the γδ TCR is different from the 'conventional' selection of MHC restricted $CD4^+$ and $CD8^+$ T cells, and this role appears to vary greatly across different γδ T cell subsets [6,19–23]. Indeed, in contrast to αβ T cells that leave the thymus as naive antigen-inexperienced T cells, functional maturation and pre-programming of γδ T cells may already occur in the thymus [24,25], with different γδ T cell subsets as marked by particular Vγ usage showing distinct TCR signal strength requirements for their functional differentiation [18,23]. However, the fact that Vγ5/Vδ1 and Vγ6/Vδ1 TCR sequences are present at the DNA level in the foetal thymus of $TCR\delta^{-/-}$ mice suggests that the corresponding TCR rearrangements are not necessarily a result of clonal thymic selection [26]. Other cells in the thymus, such as medullary thymic epithelial cells (mTECs), may play an important role in γδ T cell development. Indeed, murine Vγ5/Vδ1 T cell progenitors contribute to the emergence of $Aire^+$ mTECs that in turn foster Skint-1-dependent DETC progenitor maturation and the emergence of an invariant DETC Vγ5Vδ1 repertoire [27]. In addition, Aire may have an inhibitory role in the development of IL-17 producing invariant Vγ6/Vδ1 T cells in the mouse [28].

The majority of human blood γδ T cells express a Vγ9JγPCγ1 chain paired with a Vδ2 chain (Vγ9/Vδ2 T cells; nomenclature according to Lefranc & Rabbitts [29]), while γδ T cells in tissues such as the intestine, skin or liver are enriched in other Vδ and/or Vγ chains [4–6]. The high prevalence of Vγ9/Vδ2 T cells showing a restricted TCR repertoire in the adult peripheral blood has been attributed to extrathymic expansion in response to environmental and pathogenic microbes [30], with a striking prevalence of a single germline-encoded CDR3γ sequence in adults [31,32]. However, functionally programmed Vγ9/Vδ2 T cells expressing a semi-invariant TCR already dominate in second trimester foetal blood, before post-natal microbial exposure [33], therefore arguing against ligand-driven focussing of the TCR repertoire after birth. As for murine foetal Vγ5/Vδ1 T cells, the role of putative TCR ligands in thymic selection of human Vγ9/Vδ2 T cells remains to be investigated, and further studies are clearly needed to address how γδ T cell subsets acquire their TCR and functional specificities.

2.2. Ligand-dependent peripheral expansion

A change in the TCR repertoire, especially of the variable CDR3 region, upon infection or in response to other stimuli can be regarded as evidence of functional involvement of the TCR, and thus cognate TCR-ligand interaction [34,35]. For instance, human Vγ9/Vδ2 T cells expand in numerous microbial infections [3,36].

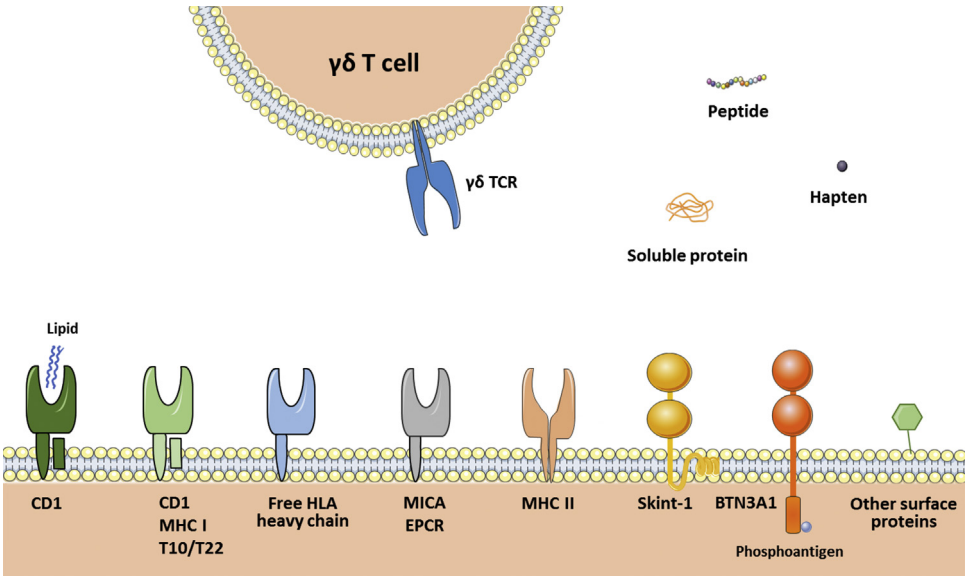

Fig. 1. Different classes of proposed and confirmed γδ T cell ligands. Examples include classical MHC class I (HLA-B*5802, free HLA heavy chain) and class II molecules (I-E^k, I-A^d), members of the CD1 family (CD1c, CD1d) that may or may not present lipid antigens, MHC and CD1 related molecules (T10/T22, Qa-1, MICA, EPCR), butyrophilin-like molecules (Skint-1, BTN3A1), other surface-bound proteins (hMSH2, EphA2, annexin A2), soluble proteins (HSV-gI, phycoerythrin, histidyl-tRNA synthetase), 'phosphoantigens' (HMB-PP, IPP), haptens (cyanine 3, 4-hydroxy-3-nitrophenyl acetyl) and free peptides (insulin B:9-23 and others).

However, it is not clear whether there is a preferential selection of certain CDR3 regions upon encountering pathogens, especially within the polyclonal CDR3δ repertoire using the Vδ2 gene segment [31,33,37]. γδ T cells also respond towards human cytomegalovirus (CMV), showing striking expansions in the blood of organ transplant recipients [35,38–40]. These expansions are limited to $Vδ1^+$, $Vδ3^+$ and $Vδ5^+$ T cells (often referred to as $Vδ2^{neg}$ T cells) and accompanied by restrictions in the CDR3 repertoire, especially of the CDR3δ using the Vδ3 gene segment [38]. While unfocused polyclonal γδ TCR repertoires are present in γδ T cells derived from term delivery cord blood [34,40], CDR3 repertoires become highly restricted upon congenital CMV infection *in utero*, with a striking enrichment of a public and invariant Vγ8/Vδ1 TCR that contains germline-encoded CDR3γ and CDR3δ [40]. Thus, different human γδ T cell subsets appear to react towards different types of pathogens, and in the case of CMV infection, substantial changes in the CDR3 repertoires strongly indicate an involvement of cognate TCR-ligand interactions. Of note, TCR biases have also been observed within MHC-restricted αβ T cell responses, for instance towards herpes viruses, including CMV [9,10]. Yet, with only a very limited number of γδ TCR ligands and structures defined so far it remains unclear as to how much these antigen-specific αβ TCR biases compare to the highly skewed γδ TCR repertoires [34,35,40].

Clonal selection of particular TCRs is a feature of adaptive immunity shared with αβ T cells and may indicate the generation of γδ T cell memory [34]. Recent studies in mouse models have indeed provided evidence for the existence of memory responses by γδ T cells [41–45], expanding previous observations in primates and in cattle [46–48]. In particular, two groups independently demonstrated an involvement of TCR signalling, presumably as a result of TCR-ligand interactions, in the generation of γδ T cell memory, with preferential enrichments in the usage of specific Vγ and Vδ chains [43,44]. Yet, CDR3 sequences were not investigated in these studies, thus calling for further in-depth analyses of recall responses by γδ T cells. Even more, irrespective of the substantial progress in our understanding of changes in the γδ TCR repertoire during development and as a result of homeostatic or infection/stress-related expansion in the periphery [6,14,34,35,48], there are remarkably few examples of γδ T cell ligands that have been implicated in such processes.

3. Monomorphic yet diverse ligands: down in the groove?

The unexpected discovery of γδ T cells in the mid 1980s immediately posed questions as to the nature of the target antigens these cells recognise. Strikingly, the compounds that have been proposed or confirmed as γδ T cell ligands since then span a staggering range of diverse molecular structures [6,49–52]. Of note, and in stark contrast to the highly polymorphic nature of the MHC class I and class II complexes that restrict αβ T cell responses, the vast majority of γδ T cell ligands reported thus far are non-polymorphic in nature.

3.1. Recognition of MHC-related molecules

Most research on γδ T cells so far has used methodologies that were originally developed and successfully applied to αβ T cells, such as immunisations of mice with MHC-mismatched cells, utilisation of transfectant APCs expressing defined antigen-presenting molecules and stainings with antigen-loaded tetramers. Perhaps not surprisingly, such approaches have led to the identification of γδ T cell clones and receptors that were reactive with classical and non-classical MHC molecules. The corresponding ligands included structures such as the murine MHC class II molecules I-E^k and I-A^d [53,54], as well as the MHC class Ib molecules T10/T22 [55,56] and Qa-1 [57] in the mouse, and MICA in humans [58] (Fig. 1).

A number of investigators also characterised CD1-restricted γδ T cells in the mouse [59] and in humans [60–66], including a peculiar T cell clone expressing a δ/αβ TCR [67]. These reports have greatly advanced our understanding of γδ T cell responses in autoimmunity and infection, and may be taken as indication that a considerable proportion of γδ T cells is reactive to MHC and MHC-related molecules [52]. However, it is important to bear in mind that most of these discoveries were based on preconceived ideas using defined ligands to identify the corresponding TCRs. Nevertheless, the importance of MHC-related molecules has been underlined further by the recent identification of γδ T cell clones recognising endothelial protein C receptor (EPCR) [68], HLA-B*5802 [69] and $β_2$-microglobulin-free HLA heavy chain [70] (Fig. 1).

Unexpectedly, many γδ T cell responses to MHC-like molecules turned out not to be strictly dependent on the presentation of specific peptidic or non-peptidic epitopes, unlike the fine-tuned

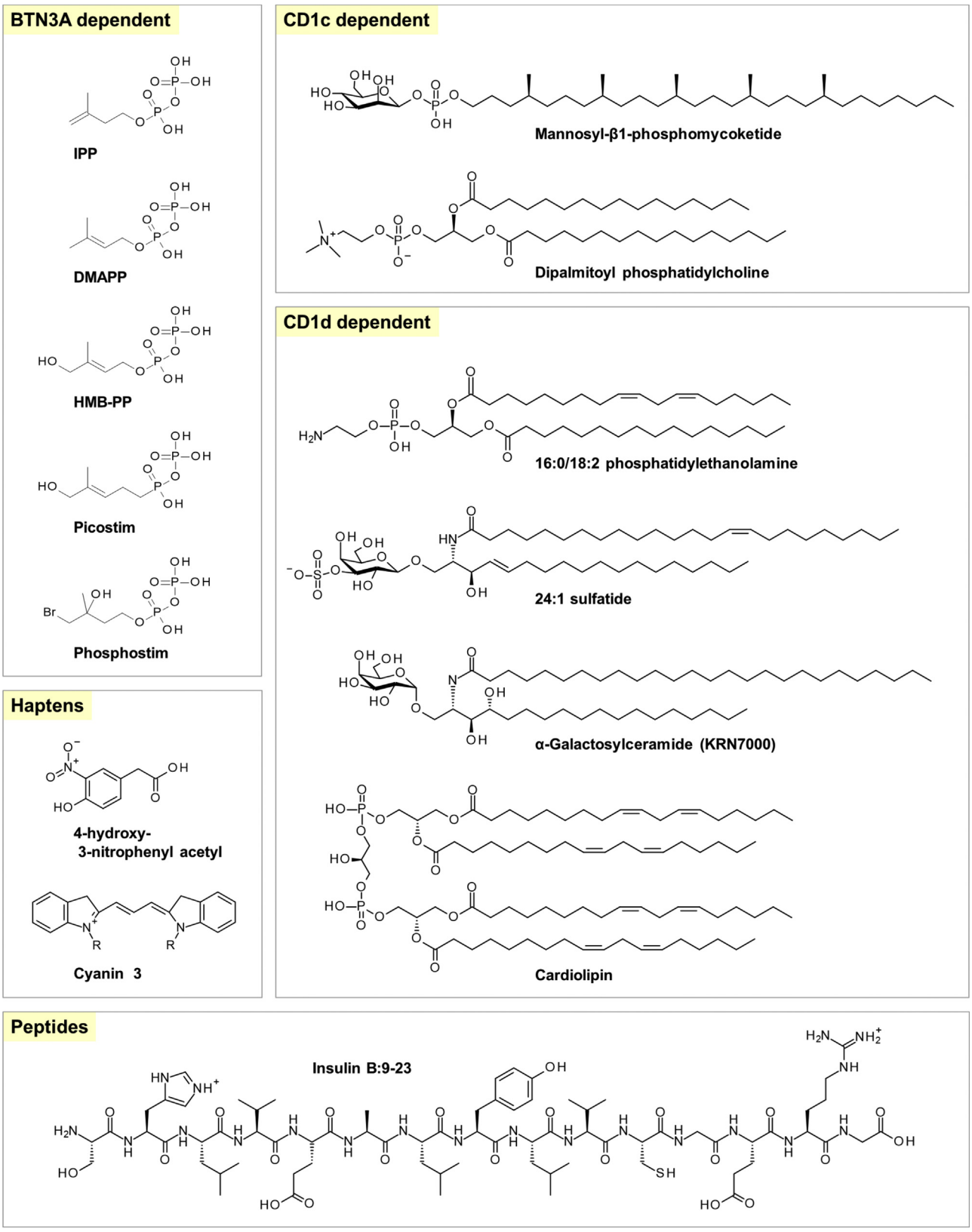

Fig. 2. Chemical structures of low molecular weight molecules recognised by γδ T cells. Examples include haptens and peptides that may bind the γδ TCR directly; 'phosphoantigens' that are recognised in the context of BTN3; and different classes of lipids that are presented by CD1c and CD1d.

recognition of antigens presented to αβ T cells in the context of MHC class I and II, MR1 and CD1. This is certainly the case for I-E^k [54], T10/T22 [56], MICA [58] and EPCR [68], neither of which appear to present antigens to the corresponding γδ TCRs. The case of Qa-1 is less clear, with indirect evidence pointing toward a possible presentation of antigenic peptides [71]. With regard to CD1-restricted γδ T cell responses, a range of phospholipids and glycolipids has been shown to activate certain γδ T cell sub-

sets. Such compounds include phosphomycoketide and dipalmitoyl phosphatidylcholine in association with CD1c [62,66], as well as the CD1d-presented molecules cardiolipin in mice [59], and phosphatidylethanolamine, sulfatide and α-galactosylceramide in humans [61–64,67] (Fig. 2). However, despite strong responses towards defined phospholipids, most CD1-restricted γδ T cells also respond with lower affinities to 'empty' CD1 molecules, which may or may not present yet unknown self lipids [60,65].

These findings highlight a remarkable dichotomy between γδ T cells and αβ T cells, where αβ TCRs recognise truly presented antigens in the classical sense while γδ TCRs may often respond to stress-induced 'empty' or non-presenting MHC-like molecules. Of note, in contrast to the invariant mouse Vγ5/Vδ1 and Vγ6/Vδ1 TCRs and CMV-reactive human Vγ8/Vδ1 TCR described above, most γδ TCRs recognising MHC-related molecules appear to contain N additions in their CDR3 regions, and the corresponding γδ T cell populations are typically rare [39,53,64].

3.2. Antibody-like recognition of surface-associated and soluble structures

Early reports on the responsiveness to MHC-like molecules by certain γδ T cell receptors were soon to be paralleled by the discovery of soluble and surface-bound proteins that appeared to bind directly to murine and human γδ TCRs. These findings in fact led some authors to liken the recognition of these potential ligands by γδ T cells to the way immunoglobulins recognise their targets antigens, which typically constitute three-dimensional epitopes on larger molecules [72]. The prime example of a protein that is recognised directly by γδ T cells, in the absence of APCs, is the herpes simplex virus glycoprotein I (HSV-gI) that specifically activates a murine Vγ2/Vδ8 T cell clone and may thus contribute to the γδ T cell-mediated protection against HSV infection in mice [73] (Fig. 1). As with HSV-gI specific γδ T cells, the responsiveness of an autoreactive human Vγ3/Vδ2 T cell clone from a polymyositis lesion toward histidyl-tRNA synthetase is directed in an antibody-like manner against a conformational epitope of the target antigen [74,75]. Of note, this Vγ3/Vδ2 TCR also cross-reacts with bacterial aminoacyl-tRNA synthetases and *E. coli* translation initiation factor 1.

The human MutS homologue 2 (hMSH2), a nuclear DNA mismatch repair protein that can be expressed ectopically on tumour cells, represents another potential protein ligand for certain human γδ T cells [76]. However, as hMSH2 appears to interact with both the γδ TCR and NKG2D the precise role of the γδ TCR in recognising tumour-associated hMSH2 remains to be resolved. More recent examples of potentially stress and infection-regulated self proteins include annexin A2 and ephrin receptor A2 (EphA2), which are recognised by human $V\delta2^{neg}$ T cell clones derived from CMV infected individuals [69,70,77] (Fig. 1).

Finally, phycoerythrin (PE) is a fluorescent molecule in cyanobacteria and red algae that is recognised by a small proportion of γδ T cells in humans, mice and cattle [78]. Although there may not be a relevant pathogen that produces PE, it is the first described ligand that activates γδ T cells in different species, albeit with no apparent sequence similarity between PE-specific γδ TCRs in humans and mice. PE is also the first soluble protein that allows to conveniently track and analyse antigen-specific γδ T cells in the mouse and therefore has enormous potential in experimental models.

In addition to larger proteins, some γδ T cells also recognise smaller molecules, which are believed to bind directly to the TCR, in the absence of APCs [79]. One such candidate is the insulin B:9-23 peptide that is recognised in a dimerised form by murine γδ T cells, possibly as a conformational structure rather than a linearised peptide sequence [80] (Fig. 1). Further self and non-self molecules that have been described to activate human, murine or bovine γδ T cells include peptides derived from heat shock proteins, mycobacterial antigens, tetanus toxin, listeriolysin O and immunoglobulin λ light chain [79,81], as well as the haptens cyanine 3 and 4-hydroxy-3-nitrophenyl acetyl [82] (Fig. 2). In the majority of cases, especially for endogenous self peptides, the physiological context leading to the availability of such soluble molecules as potential ligands for the γδ TCR remains to be elucidated.

3.3. The peculiar case of phosphoantigens

The majority of human and primate Vγ9/Vδ2 T cells responds rapidly to small phosphorylated molecules *in vitro*, often referred to as 'phosphoantigens' [3]. By far the most potent of these compounds is the microbial metabolite (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), which is produced by many Gram-positive and Gram-negative bacteria as well as malaria parasites and *Toxoplasma gondii* [3,36] (Fig. 1). Other compounds with activity on Vγ9/Vδ2 T cells, albeit at levels that can be several magnitudes above the minimum effective concentration of HMB-PP, include the ubiquitous metabolites isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which are present in all prokaryotes and eukaryotes, and related synthetic molecules such as monoethyl phosphate, bromohydrin pyrophosphate (Phosphostim) and a pyrophosphonate analogue of HMB-PP (Picostim) [3,83] (Fig. 2). Furthermore, the reactivity of Vγ9/Vδ2 T cells toward aminobisphosphonate drugs such as alendronate, pamidronate and zoledronate and toward natural and synthetic alkylamines can be explained by the intracellular accumulation of IPP, DMAPP and byproducts such as the AMP conjugate of IPP, ApppI, thereby rendering treated target cells susceptible to recognition by Vγ9/Vδ2 T cells [83–85]. In addition to its intracellular accumulation, IPP can be released by zoledronate-treated dendritic cells into the microenvironment where it becomes available to uptake by other cells and/or activation of γδ T cells [83,86]. But are 'phosphoantigens' true γδ TCR ligands? Originally thought to bind to the γδ TCR directly [87] and possibly 'presented' in the context of accessory proteins including mitochondrial F1-ATPase [88], the recent discovery of butyrophilin-3 (BTN3) as crucial restricting element rather points toward an indirect recognition of 'phosphoantigens' [89]. Of note, the presence of Vγ9/Vδ2 TCRs may not be restricted to higher primates. While being absent in mice, rats, rabbits, cattle and other farm animals, recent findings suggest that functional Vγ9/Vδ2 T cells and the reactivity toward 'phosphoantigens', alongside BTN3, may also be present in alpacas [90]. Such observations indicate that this microbe-responsive γδ T cell population may have arisen early during evolution of placental mammals and later on been lost in various groups including rodents [91].

3.4. The role of butyrophilins

Recent studies demonstrated that the BTN3 isoform, BTN3A1, is essential for Vγ9/Vδ2 T cell responses to HMB-PP, IPP and aminobisphosphonate-treated cells [89,92]. Initially proposed as a 'phosphoantigen' presenting molecule [92], a growing body of biochemical and structural evidence identified an unexpected 'phosphoantigen' binding site in the intracellular B30.2 (PRY/SPRY) domain of BTN3A1 [93–95]. In essence, BTN3A1 appears to convert a peculiar microbial (HMB-PP) or stress-related (IPP) non-peptidic signal into a rather common biological phenomenon, namely the recognition of a cell surface-associated and possibly conformational epitope that is somehow sensed by Vγ9/Vδ2 T cells [98] (Fig. 1). While the related isoforms, BTN3A2 and BTN3A3, are somehow involved in this process [95] the exact mechanism remains to be defined. BTN3 has consequently replaced 'phosphoantigens' as candidate ligand for Vγ9/Vδ2 T cells although it may require

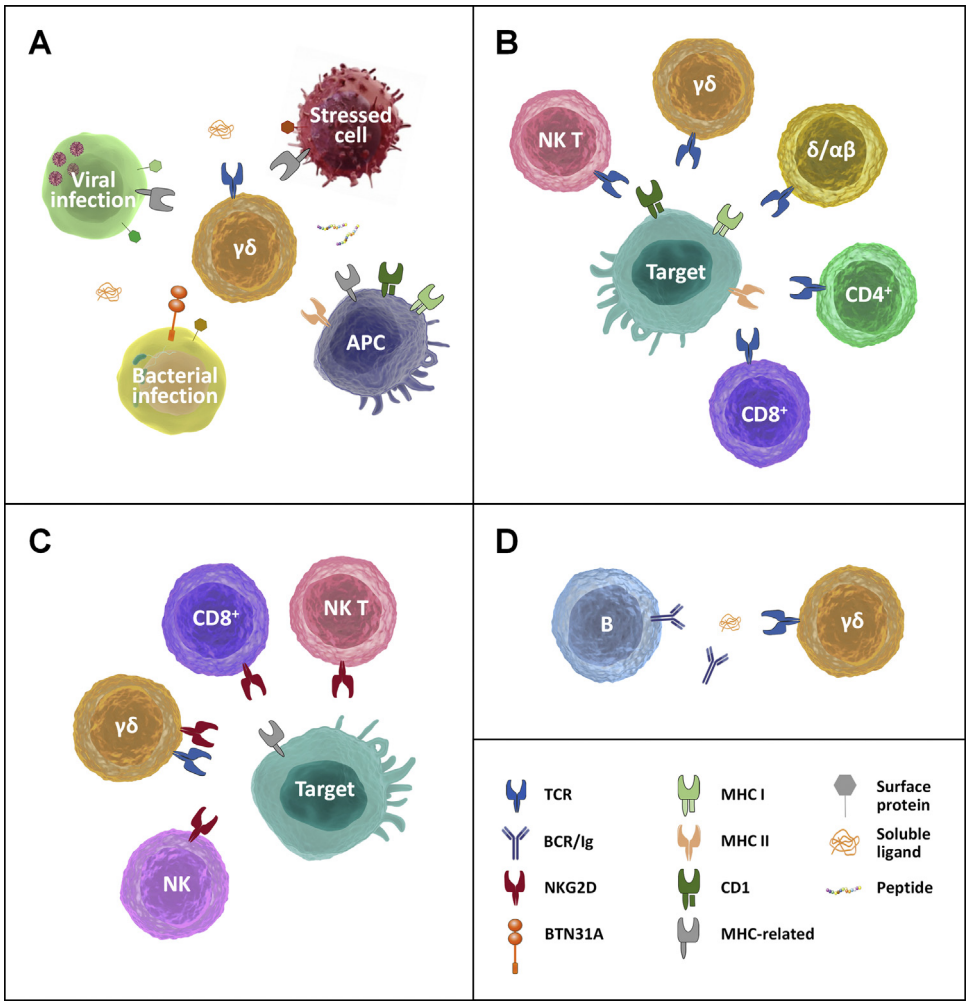

Fig. 3. Physiological context of γδ T cell ligand recognition. (*A*) Recognition of ligands in different physiological settings, ranging from ligand presentation by APCs to recognition of stressed and infected cells and direct binding of soluble molecules. (*B–D*) Overlapping recognition of stress and infection related ligands by γδ T cells and by immune receptors expressed by other cells. Examples for such promiscuous γδ T cell ligands include, but are not limited to, MHC and CD1 family members that are recognised by the TCRs of conventional and unconventional T cells (B); stress ligands such as MICA/B that are recognised by NKG2D on T cells and NK cells (C); and soluble B cell antigens such as PE and targets of autoantibodies such as tRNA synthetases (D). BCR/Ig, B cell receptor/immunoglobulin.

accessory molecules and may not be recognised directly by the Vγ9/Vδ2 TCR [95–99]. Of note, the immunological role of BTN3A1 may extend beyond the regulation of γδ T cell responses [100,101].

The clear role for BTN3 in driving human Vγ9/Vδ2 T cell responses evokes seminal discoveries in other systems amounting to the realisation that the family of butyrophilin-like (BTNL in humans, Btnl in mice) proteins plays a pivotal part in shaping the γδ T cell compartment [102–104]. The best studied Btnl member, Skint-1, is crucially important for the maturation of murine thymocytes and the appearance of Vγ5/Vδ1 DETCs in the epidermis [105,106]. This process requires thymic and epidermal expression of Skint-1, although it is not clear whether Skint-1 indeed constitutes a direct ligand for the Vγ5/Vδ1 TCR [106,107] (Fig. 1). Intriguingly, there may also to be a role for Skint-3 and Skint-9 in modulating DETC function, especially during wound repair [108]. In analogy to the Skint-1 restricted development of Vγ5/Vδ1 T cells in the mouse epidermis, joint expression of the related proteins Btnl1 and Btnl6 by murine enterocytes is required for the extrathymic selection of intestinal Vγ7$^+$ T cells [104]. Similarly, human BTNL3 and BTNL8 appear to jointly induce selective TCR-dependent responses by Vγ4$^+$ T cells derived from the human colon [104].

These groundbreaking findings demonstrate that different butyrophilins influence the development of specific γδ T cell populations characterised by distinct Vγ chains in mice and in humans, and identify a fundamental selection principle that is likely to be applicable to other γδ T cell subsets and other species. How the different members of the butyrophilin family achieve this remains to be elucidated, especially as to whether they bind the γδ TCR directly or merely constitute critical co-factors. The fact that the majority of Btnl and BTNL proteins (with the prominent exception of Skint-1) possess intracellular B30.2 domains also raises the possibility that as yet unknown accessory molecules are involved in shaping the γδ T cell repertoire. B30.2 domains not only sense HMB-PP and IPP in the case of BTN3A1 but also confer pattern recognition receptor-like functions to tripartite motif proteins such as TRIM5α and TRIM21 that are evolutionarily linked to butyrophilins [103,109a]. While the selection of Vγ7$^+$ T cells by Btnl1/Btnl6 appears to be independent of microbial or food antigens [104], the self and non-self metabolites and proteins potentially interacting with butyrophilins clearly deserve closer attention.

4. Context of ligand expression: by a simple twist of fate

4.1. Sensing self, stressed self and non-self

The physiological contexts in which γδ T cell ligands become accessible is key to understand the role of γδ T cells in the immune system. The chemical and conformational structures that γδ T cells respond to cover molecules associated with infection, stressed tissues and tumours as well as with the healthy status, and are far more diverse than the relatively narrow range of MHC and CD1-presented αβ T cell antigens (Fig. 3A). γδ T cells sense these ligands by patrolling blood and endothelial and mucosal surfaces for pathogen pattern recognition, and as tissue-resident cells by monitoring tissue integrity and vitality [4–6,36]. Pathogens may actually influence this tissue monitoring by targeting γδ T cell ligands. In this context, it has recently been shown that human papillomavirus oncoproteins induce a decrease in epidermal Skint1 expression, which is associated with a change in morphology and reduced density of the associated Vγ5/Vδ1 DETC [109b]. Of note, besides the TCR, γδ T cells can also express other activating receptors such as NKG2D, NKp30 and CD16 [110], which may complement or even replace TCR signalling in different contexts. For instance, the role DETCs play in skin immune surveillance is at least in part exerted via recognition of stress-induced NKG2D ligands [111]. The relevance of the majority of the γδ TCR ligands discussed in this review therefore remains ill-defined, especially since many are only recognised by a very small proportion of the total γδ T cell population [55,78], or by seemingly rare γδ T cell clones found in individual patients [68–70,75].

Non-self molecules sensed by human or murine γδ T cells include proteinaceous and non-proteinaceous molecules as diverse as viral HSV-gI [73], algae-derived PE [78], staphylococcal superantigens [112,113], listerolysin and tetanus toxin peptides [79], pollen-derived phosphatidylethanolamine [61], bacterial cardiolipin [59], mycobacterial phosphomycoketide [62] and HMB-PP [36], together with further unidentified microbial compounds [62,114–116]. Bovine γδ T cells recognise a range of antigens derived from *Mycobacterium bovis*, *Leptospira* and *Anaplasma* although the precise role of the γδ TCR in such responses and the contribution of WC1 as co-receptor and pattern recognition receptor requires further characterisation [81,117,118]. Of note, cardiolipin may also derive from the mitochondria of stressed or damaged host cells [59], and the role of HMB-PP may be mimicked by IPP as host-derived self ligand, despite its much lower bioactivity and B30.2 affinity compared to HMB-PP [83,93]. In addition, γδ T cells may respond to both CD1-presented self and non-self lipids [6,51,52], and there appears to be cross-reactivity between bacterial and mammalian heat shock proteins [79] and aminoacyl-tRNA synthetases [75]. The distinction between self and non-self may thus not be as clear-cut as the above list of ligands insinuates, which raises further questions about the physiological context in which the corresponding γδ T cell populations become activated.

It has been proposed that some γδ TCRs can respond to upregulation of 'stress proteins' upon infection, cell transformation or other conditions, although examples of such a recognition mode are limited [4–6,77,119]. Alternatively, ligands may be constitutively expressed, but it is the molecular context that will define their γδ T cell activation potential. For instance, EPCR, the ligand for a γδ T cell clone that was expanded in a CMV infected transplant recipient, is actually not upregulated upon CMV infection [68]. CMV infection rather appears to result in the induction of other factors that, together with EPCR, form a 'multi-molecular stress signature' [68]. Similarly, the γδ TCR of mouse DETCs appears to be continuously activated within the epidermis, suggesting that the corresponding ligand is constitutively expressed by keratinocytes [120]. However, cellular stress may provoke changes in the expression and/or the conformation of the DETC ligand, possibly in conjunction with additional factors [121]. The importance of further co-factors is also underlined by the fact that both BTN3A1 and IPP are ubiquitously expressed by human cells [91,103]. The exact conditions under which endogenous IPP levels may exceed a possible threshold for stressed cells to become stimulatory to Vγ9/Vδ2 T cells whilst preventing autoreactivity toward metabolically active healthy tissues remain to be defined [3,83]. Clearly, γδ T cell responses to self ligands require carefully balanced control mechanisms.

4.2. Implications for pathology and diagnosis

The ability of γδ T cells to sense structures associated with tissue stress, transformation and infection has direct consequences in the clinic. Ligand-dependent γδ T cell responses may contribute to protective immunity against pathogens [73,122] and tumour immune surveillance [76] but may also drive inflammation-related tissue damage [123] and autoimmune disease [124,125]. For instance, IL-17 producing γδ T cells play a pathogenic role in experimental models of psoriasis [126,127], and IL-17$^+$ Vγ9/Vδ2 T cells and common CDR3γ sequences have been observed in psoriatic lesions of patients [128,129], suggesting ligand-driven local recruitment and/or expansion in the skin. γδ T cells may also drive the pathology in further autoimmune diseases where certain γδ T subpopulations are locally enriched, possibly in response to self ligands such as sulfatide in the case of multiple sclerosis [63,124,130] and histidyl-tRNA synthetase in the case of polymyositis [74,75]. Vice versa, pathogens may target tissue-restricted ligands and thereby affect the corresponding resident γδ T cell subset [109b]. In mice deficient in the autoimmune regulator Aire, which functions as a master transcriptional regulator of thymic gene expression, foetal IL-17$^+$ Vγ6/Vδ1 T cells are increased and contribute to retinal inflammation and degeneration [28]. Also, immunodeficient patients with mutations in the *AIRE* gene show elevated percentages of Vγ9/Vδ2 T cells producing IL-17 [28]. Notwithstanding this apparent contribution of Aire to immune tolerance by limiting IL-17 production by γδ T cells that are generated in early life in both mice and humans [33,131], it remains unclear whether Aire-dependent effects on γδ T cell ligand expression in the thymus play a role in selecting autoreactive γδ T cells [28]. With respect to cancer, γδ T cells have well established protective roles in tumour surveillance and immunotherapy, in particular because of their potent cytotoxicity and IFN-γ production [4–6]. However, recent studies have also revealed tumour-promoting functions that are linked to IL-17 producing γδ T cells [109b,132]. How much of such protective or detrimental responses are driven by γδ T cell ligands is unclear.

The exquisite specificity of human Vγ9/Vδ2 T cells for microbial derived HMB-PP may be exploitable for diagnostic and prognostic purposes to help identify the causative pathogen in patient samples well before conventional culture results become available [133]. Infections caused by HMB-PP producing organisms tend to be associated with higher frequencies of Vγ9/Vδ2 T cells than infections caused by HMB-PP deficient organisms. This is the case in the blood of patients with acute sepsis [134] but is particularly pronounced at the site of infection [123,135]. A similar diagnostic potential may reside within the unique reactivity of human Vδ2^{neg} T cells to CMV infections [136–138]. In particular, longitudinal monitoring of Vδ2^{neg} T cell profiles shows promise as prognostic marker for the prediction of CMV infection resolution and treatment responses in kidney transplant recipients [139]. Finally, recent reports suggest that the expansion of certain Vδ clonotypes in patients with acute myeloid leukaemia may correlate with disease outcome [140], although the specificity of those γδ T cell clones remains to be defined.

It is interesting to note that a significant number of γδ T cell ligands are also recognised by other immune receptors (Fig. 3B–D).

Intriguingly, there are cases of autoantibody production and expansion of γδ T cells possessing the same specificity, for instance in patients with multiple sclerosis and polymyositis [63,74,75,124]. Such recognition of the same targets by immunoglobulins and γδ T cells may result from specific γδ T cell help to B cells [141], which is supported by the observation of a considerable overlap between γδ TCR specificities and natural antibodies [142]. The significance of this redundancy for protection and pathology has not been addressed as yet.

4.3. Implications for therapy and vaccination

A better understanding of γδ T cell ligands will ultimately guide the potential application of γδ T cell based therapies in the clinic. The monomorphic nature of γδ T cell ligands and their independence of the underlying MHC haplotype is in fact ideal for vaccine development and 'off the shelf' cellular therapies. However, given the limited numbers of defined ligands with clear disease relevance and the rare nature of the corresponding γδ T cell clones, there is only scarce evidence for a successful stimulation of γδ T cell responses with defined ligands *in vivo* [82,143].

Most progress in this context has been made thanks to the reactivity of human and primate Vγ9/Vδ2 T cells to 'phosphoantigens'. In cynomolgus macaques, stimulation with HMB-PP itself, or with synthetic HMB-PP analogues, induces a strong expansion of Vγ9/Vδ2 T cells in the blood [144] and their accumulation at mucosal sites including the lungs of treated animals, and attenuates local tuberculosis and plague lesions [122,145]. While these findings demonstrate that protective immunity against microbial pathogens can be achieved by directly harnessing γδ T cells, administration of 'phosphoantigens' alongside mycobacterial antigens did not have any adjuvant effect *in vivo* and did not boost concominant vaccine-induced αβ T cell responses [146]. However, activation of Vγ9/Vδ2 T cells did enhance antibody-dependent cell-mediated cytotoxicity in cynomolgus macaques treated with the anti-CD20 depleting antibody rituximab [147]. In humans, Vγ9/Vδ2 T cells can readily be targeted using aminobisphosphonates such as zoledronate, most likely via indirect accumulation of IPP and DMAPP in endocytic cells including monocytes, osteoclasts and tumour cells [132,148–150]. Alternatively, agonist antibodies against BTN3 may specifically sensitise tumour cells to Vγ9/Vδ2 T cell cytotoxicity although this has thus far only been demonstrated in murine xenotransplantation models [151], and the safety of antibodies targeting ubiquitously expressed BTN3 in the body needs to be established in humans. These reports provide proof-of-concept evidence that γδ T cell responses can be manipulated efficiently if the mode of recognition is known. It will now be interesting to test whether other ligands are similarly capable of stimulating distinct γδ T cell subpopulations *in vivo*. Of note, once activated and/or expanded, the anti-tumour potential of γδ T cells may at least in part depend on their recognition of tumour targets via NKG2D and other natural killer receptors, and the contribution of γδ TCR ligands especially in patients receiving adoptively transferred γδ T cells is unclear as yet [132,148,149].

In other scenarios, specific targeting of γδ T cell ligands in the clinic may allow a suppression of excessive γδ T cell-driven inflammation in infectious or autoimmune diseases. For instance, anti-BTN3 antibodies effectively abrogate Vγ9/Vδ2 T cell responses to microbial pathogens and may thus be able to limit fibrotic scarring of local tissues in vulnerable patient groups [123]. A similar neutralisation of inappropriate Vγ9/Vδ2 T cell responses may be achieved by using TCR-specific variable domains of naturally occurring H chain-only antibodies (nanobodies) [99]. It is thus conceivable that specific masking of stress-induced and/or disease-specific γδ T cell ligands can reduce the recognition of target tissues by pro-inflammatory γδ T cells, which may block the detrimental role these cells can play in autoimmune disorders, transplantation and ischemia-reperfusion injury [152–154].

5. Outlook: there must be some way out of here

The past few years have seen a wealth of data regarding the TCR repertoires of distinct γδ T cell populations in health and disease and a growing list of confirmed and proposed ligands in different species [6,49–52]. Yet, the relevance of the often restricted TCR usage and the chemical diversity in γδ T cell ligands remain largely unclear, and only few structural studies have confirmed definite ligand recognition by the TCR [56,63,64]. There are also open questions pertaining to the specificity of the γδ TCR and the role their ligands play in thymic selection, homeostasis and disease. Moreover, instead of recognising a single ligand, it is conceivable that γδ T cells may show the same cross-reactivity towards a considerable number of different ligands that is well-established for αβ T cells [155]. The existence of multiple specificities of self and non-self reactive γδ TCRs has been discussed before [50], albeit the implications of such a phenomenon for the thymic selection of cross-reactive γδ TCRs and the prevention of potentially autoaggressive responses remain to be addressed.

Most importantly, there is no unbiased approach to identify novel ligands and potential restriction elements. For instance, the extent of γδ TCRs that are restricted by MHC-like molecules is not clear. Whilst a proportion of γδ T cells can indeed be stained with tetramers and respond to known and unknown ligands [52], the identification of CD1 restricted γδ TCRs may ultimately be the result of a technological bias and may not be representative of the γδ TCR repertoire as a whole. This caveat notwithstanding, tetramer-positive γδ T cells may actually be enriched in particular tissues such as the liver and are likely to play a prominent role *in vivo* [156]. Another bias may inevitably be introduced during prolonged cloning procedures that select for clones with high proliferative capacity rather than clones with relevant effector function *in vivo*. Similarly, approaches to screen infection-associated γδ TCRs based on their cross-reactivity with transformed and stressed cells may eventually only yield self ligands whilst ignoring foreign structures [68]. The inherent limitations of current methodologies call for innovative, unsupervised methods that cover the breadth of possible ligands.

High-throughput sequencing has transformed our ability to examine antigen receptor repertoires, but this technology is only starting to be applied to γδ T cell clonotyping [22,31,34,35,129]. It is expected that in-depth analyses of CDR3γ and CDR3δ repertoires of *ex vivo* samples will provide a more unbiased insight into ligand-driven γδ T cell responses during development and towards stress-related and infectious stimuli, as well as into the role of innate-like, invariant and public γδ TCR sequences [22,31,33–35,40]. γδ TCRs that are of demonstrable relevance *in vivo* can then be subjected to ligand identification strategies using functional blocking antibodies [68] or γδ TCR tetramers [121,157]. In addition, single-cell sequencing will greatly expand the current knowledge of the association between particular CDR3 sequences of a γδ T cell and its effector functions including programmed cytokine gene expression [158]. Such approaches will ultimately aid the discovery of the corresponding TCR ligands.

γδ T cells have been conserved as a third type of lymphocyte, alongside αβ T cells and B cells, since the emergence of jawed vertebrates 400 million years ago. The dependence of cellular immunity on a tripartite system of three distinct lymphocyte populations goes back even further as it is already found in lampreys [159]. The existence of profound species-specific differences in TCR repertoires, anatomical locations of γδ T cell subsets and the variable nature of the ligands they respond may therefore reflect strong

evolutionary pressure and rapid adaption within the γδ T cell compartment. Nevertheless, there are molecules that are recognised by γδ T cells across different species and appear to constitute evolutionarily ancient ligands. Such signals include CD1d as restricting element for lipid antigens in humans and mice [6]; phycoerythrin as activator of minor γδ T cell subsets in humans, mice and cattle [78]; and BTN3/HMB-PP, which may activate Vγ9/Vδ2 T cells not only in humans and other primates but also in alpacas [91]. Further work in species other than primates and rodents will help define the relevance of functionally overlapping and divergent γδ T cell responses [90,160,161].

In conclusion, the role of γδ T cells in the immune system has remained enigmatic over the past three decades, mostly due to the paucity of ligands identified so far and their failure to conform to classical αβ T cell-centric models. However, the combination of high through-put sequencing, bespoke animal models and access to well defined patient cohorts and tissue banks is beginning to shine light on one of the remaining blind spots in immunology. Understanding better the molecular nature of γδ T cell ligands and the physiological contexts in which they become available will finally allow the integration of γδ T cell mediated responses into a comprehensive view of innate and adaptive immunity. The times they are a-changin'.

Conflict of interest statement

The authors declare no competing financial interests.

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